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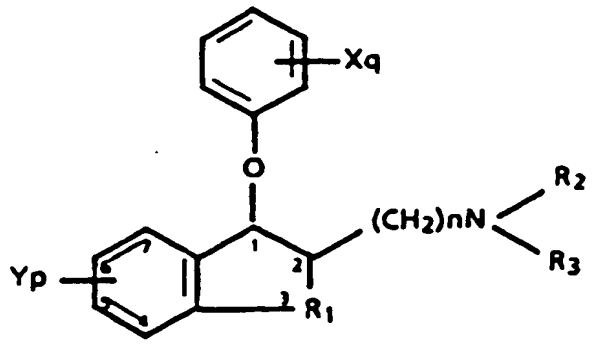
Description

The present invention provides novel compounds of the formula (1)



wherein

R_1	is a C_1-C_3 alkylene,
n, p and q	are each independently 0, 1 or 2,
Y and X	are each independently (C_1-C_6)alkyl, (C_1-C_6) alkoxy, hydroxy, CF_3, halogeno or when p or q are 2 and each of the Y or each of the X groups are on adjacent aryl carbon atoms, both of the X or both of the Y groups can be taken together to form a methylenedioxy moiety,
R_2 and R_3	are each independently hydrogen, (C_1-C_6) alkyl, aralkyl,or R_2 and R_3 taken together with the nitrogen to which they are attached are pyrrolidino, morpholino, piperidino, piperazino, or 4-methylpiperazino,

or an acid addition salt thereof.

EP-A-207600 describes a class of hydroxycycloalkanephenoxyethylamine derivatives having antidepressant activity.

GB-1,067,659 describes antidepressant compositions containing 2-chloro-9-(3-dimethylaminopropylidene)thioxanthene or 5-(3-dimethylaminopropylidene)dibenzo[a, d]cyclohepta[1,4]-diene.

R_1 is a divalent alkylene group comprised of 1 to 3 carbon atoms of straight or branched chain configuration including, for example, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-C(CH_3)_2-$, and $-CH(CH_3)CH_2-$. Where R_1 is $-CH_2-$, the compounds of formula (1) are aryloxy indanamine derivatives; where R_1 is $-CH_2CH_2-$, the compounds of formula (1) are aryloxy-1,2,3,4-tetrahydronapthylamine derivatives; where R_1 is $-CH_2CH_2CH_2-$, the compounds of formula (1) are aryloxy-5,6,7,8-benzocycloheptenamine derivatives.

The aryloxy moiety of compounds of formula (1) can be mono- or di-substituted at any feasible position(s) in the ring (when q is 1 or 2, respectively) or it can be unsubstituted (when q is 0). X is independently chosen each time it is taken so that when q is 2 the aryloxy moiety is di-substituted with the same or different substituents. Likewise, the fused-ring moiety can be mono- or di-substituted at any of the 4, 5, 6, or 7 position(s) (when p is 1 or 2, respectively) or it can be unsubstituted (when p is 0). Y is independently chosen each time it is taken so that when p is 2 the fused-ring moiety is di-substituted with the same or different substituents. R_2 and R_3 can be independent moieties or they can be taken together with the nitrogen to which they are attached to form a pyrrolidino, morpholino, piperidino, piperazino, or 4-methylpiperazino group.

As used herein, the term "lower alkyl" refers to an alkyl group comprised of 1 to 6 carbon atoms in straight, branched, or cyclic configuration. The term "lower alkoxy" refers to a lower alkyl group substituted with a single oxygen atom which is attached to the appropriate aryl carbon. The term "halogeno" refers to a fluoro, chloro, bromo or iodo substituent. The term "methylenedioxy" refers to a $-O-CH_2-O-$ moiety attached to adjacent aryl carbon atoms. The term "aralkyl" refers to an aromatic ring attached to the nitrogen atom by a C_1 to C_4 alkylene bridge. For example, the term "aralkyl" includes, but is not limited to benzyl, phenyl(C_1-C_4)alkyl and the like.

Compounds wherein R_2 and/or R_3 are CO_2Me or CO_2Et, i.e., the methyl or ethyl ester of a carboxy group,, are novel intermediates useful in the preparation of compounds of the formula (1). These esters can be made by utilizing procedures analogous to those described below for compounds of the formula (1) and by utilizing standard procedures well known and appreciated in the art.

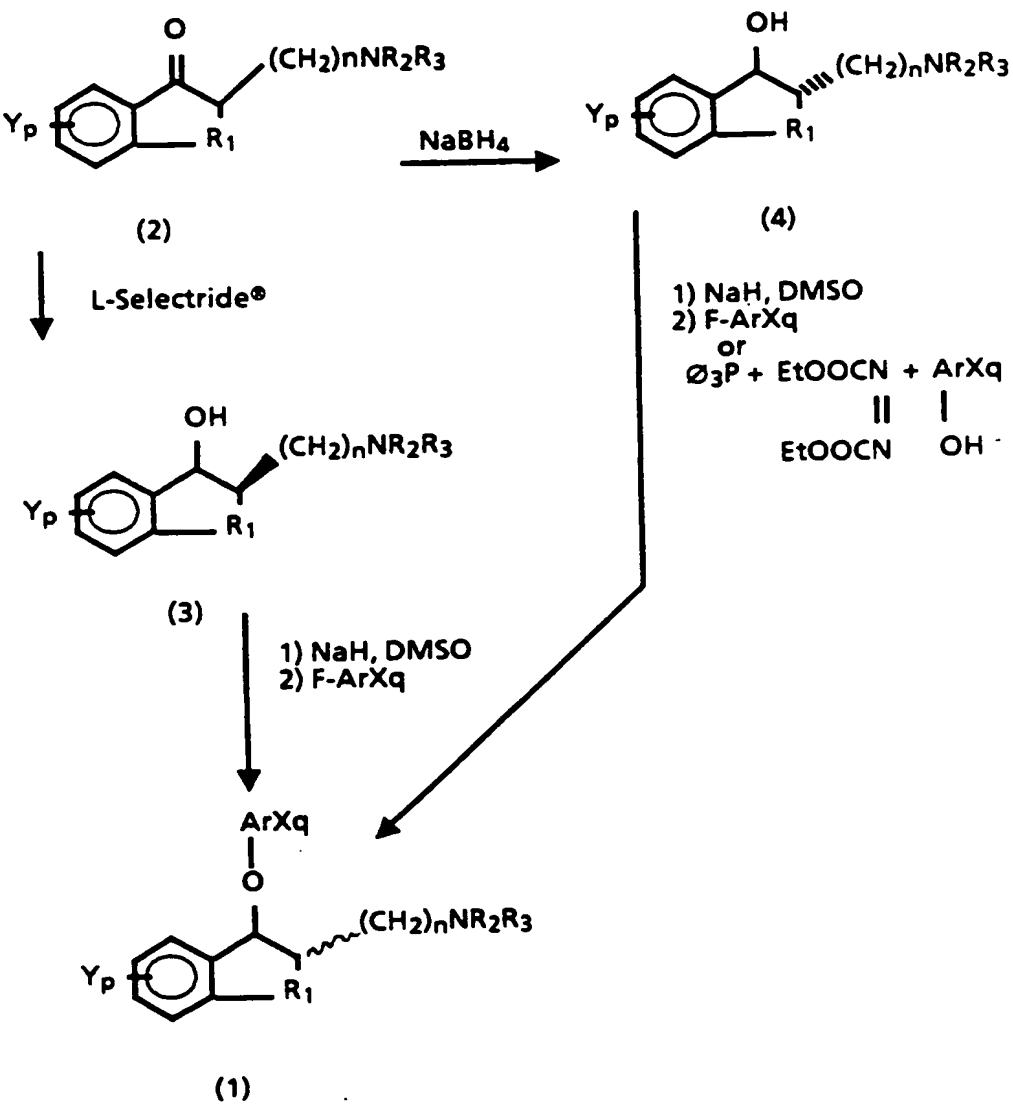
Compounds of the formula (1) can be employed as free amines or as acid addition salts thereof. The term "acid addition salts" encompasses both organic and inorganic acid addition salts including, for example, those prepared from acids such as hydrochloric, oxalic , and the like. For example, compounds of the formula (1) wherein X or Y is CF_3 can be converted to the hydrochloric acid addition salt using conventional methods well known in the art.

As will be recognized and appreciated by those skilled in the art, the compounds of formula (1) can exist in a CIS or TRANS stereoisomeric form with respect to the aryloxy moiety and the amine moiety. It is understood that the present invention encompasses both the CIS or TRANS forms individually and mixtures thereof.

In general, the compounds of formula (1) may be prepared by chemical reactions analogously known in the art, the choice of any specific route of preparation being dependent upon a variety of factors. For example, general availability and cost of the reactants, applicability of certain generalized reactions to specific compounds, and so forth, are all factors which are fully understood by those of ordinary skill in the art and all contribute to the choice of synthesis in the preparation of any specific compound embraced by formula (1). In preparing these compounds, standard procedures and techniques which are well known and appreciated by those of ordinary skill in the art are utilized.

For example, compounds of the formula (1) can conveniently be made according to the general synthetic route outlined in Scheme A.

Scheme A*



***The Yp, Xq, R_1, R_2, R_3 substituents are as previously defined.**

In general, compounds of the formula (1) can be prepared by reacting the appropriately substituted amino ketone (2) with L-Selectride®(lithium tri-O-isobutyl borohydride available from Aldrich) to give the amino alcohol (3). This generally results in the CIS isomer in substantially pure form. The sodium derivative of the amino alcohol (3) which is formed by reacting (3) with sodium hydride (NaH) in dimethylsulfoxide (DMSO) is further reacted with the appropriately substituted aryl fluoride (F-ArXq) in the presence of DMSO to give the corresponding compound of the formula (1). Again this generally results in the CIS isomer in substantially pure form or in a mixture of the CIS and TRANS isomers.

Alternatively, compounds of the formula (1) can be prepared by reacting the appropriately substituted amino ketone (2) with sodium borohydride ($NaBH_4$) which gives the amino alcohol (4) in substantially pure TRANS isomeric form. The compounds of the formula (1) can then be formed by reacting the sodium derivative of the amino alcohol (4) with the appropriately substituted aryl fluoride as described above. In the alternative, the amino alcohol (4) can be reacted with the appropriately substituted aryl alcohol (HO-ArX) in the presence of triphenyl phosphine ($Ø_3P$) and diethoxyazodicarboxylate (EtOOCN = NCOOEt). This procedure can yield compounds of the formula (1) in substantially pure CIS or TRANS forms or in a mixture thereof.

Where it is desired to resolve and isolate the CIS or TRANS stereoisomeric forms of a compound of the formula (1) from a mixture thereof, this resolution can be effected by standard procedures and techniques as are well known and appreciated in the art.

The following examples serve to illustrate synthetic procedures utilized to make compounds of the formula (1) according to the procedure outlined in Scheme A. These examples are intended to be illustrative only and are not intended to limit the invention in any way. All temperatures are in degrees Celsius.

EXAMPLE 1

CIS-2,3-dihydro-1-(2-methoxyphenoxy)-N,N-dimethyl-1H-indene-2-methanamine

STEP A: CIS-2,3-Dihydro-2-(N,N-dimethylaminomethyl)-inden-1-ol

To an ice-cooled suspension of 2.25 g (0.01M) of 2,3-dihydro-2-(N,N-dimethylaminomethyl)-1H-inden-1-one hydrochloride in 50 ml of dry tetrahydrofuran was added 25 ml of a 1M solution of L-Selectride®. The mixture was stirred for 1.5 hours and decomposed with 5 ml of 10% sodium hydroxide solution. The solvent was evaporated at reduced pressure and the residue distributed between ether and water. The ether layer was separated and extracted with dilute hydrochloric acid. Basification of the acid extract gave an oil which was extracted into ethyl acetate. Evaporation and Kugelrohr distillation at 90-100°/0.4 mm Hg gave 0.92 g (48%) of amino alcohol.

	Anal. Calcd for $C_{12}H_{17}NO$		
Fd:	C = 75.35; C = 74.86;	H = 8.96,; H = 9.00;	N = 7.32 N = 7.25

By procedures analogous to that described above, the following amino alcohols can be prepared:
CIS-2,3-dihydro-2-(N-methyl-N-phenylmethylaminomethyl)-1H-inden-1-ol
Bp 135-140°/0.3mm Hg

	Anal. Calcd for $C_{18}H_{21}NO$		
Fd:	C = 80.86; C = 80.68;	H-7.92; H = 7.95;	N-5.24 N = 5.21

CIS-6-chloro-2,3-dihydro-2-(N,N-dimethylaminomethyl)-1H-inden-1-ol
Bp 118-121°/0.3 mm Hg

	Anal. Calcd for $C_{12}H_{16}ClNO$		
Fd:	C = 63.85; C = 63.80;	H = 7.15; H = 7.30;	N = 6.21 N = 6.31

CIS-2,3-dihydro-2-(4-morpholinomethyl)-1H-inden-1-ol
Bp 119-127°/0.3 mm Hg

Anal. Calcd. for $C_{14}H_{19}NO_2$			
Fd:	C = 72.07; C = 71.81;	H = 8.21; H = 8.15;	N = 6.00 N = 5.77

TRANS-2-dimethylaminomethyl-1,2,3,4-tetrahydronaphthalen-1-ol
Bp 127-35 °/0.4 mm Hg

Anal. Calcd for $C_{13}H_{19}NO$			
Fd:	C = 76.05; C = 75.83;	H = 9.33; H = 9.21;	N = 6.82 N = 6.50

TRANS-2,3-dihydro-2-dimethylaminomethyl-inden-1-ol
m.p. 65-67 °

Anal. Calcd. for $C_{12}H_{17}NO$			
Fd:	C = 75.35; C = 75.32;	H = 8.96; H = 8.96;	N = 7.32 N = 7.26

TRANS-2,3-dihydro-6-fluoro-2-dimethylaminomethylinden-1-ol
m.p. 93-95 °

Anal. Calcd. for $C_{12}H_{16}FNO$			
Fd:	C = 68.87; C = 69.02;	H = 7.71; H = 7.84;	N = 6.69 N = 6.57

CIS-2,3-dihydro-6-methoxy-2-dimethylaminomethylinden-1-ol
Bp 102-110 °/0.3mm Hg

Anal. Calcd for $C_{13}H_{15}NO_2$			
Fd:	C = 70.55; C = 70.23;	H-8.66; H = 8.86;	N = 6.33 N = 6.20

CIS-2,3-dihydro-6-fluoro-2-dimethylaminomethylinden-1-ol
Bp 90-93 °/0.3mm Hg

Anal. Calcd. for $C_{12}H_{16}FNO$			
Fd:	C = 68.87; C = 68.82;	H = 7.71; H = 7.82;	N = 6.60 N = 6.52

CIS-2,3-dihydro-5-fluoro-2-(N,N-dimethylaminomethyl)-1H-inden-1-ol
CIS-2,3-dihydro-3,3-dimethyl-2-(N,N-dimethylaminomethyl)-6-methoxy-1H-inden-1-ol
CIS-2,3-dihydro-2-(N-ethyl-N-methylaminomethyl)-5,6-dimethoxy-1H-inden-1-ol
CIS-6-(N,N-dimethylaminomethyl)-5,6,7,8-tetrahydrobenzocycloheptene-5-ol
CIS-2,3-dihydro-6-fluoro-2-(4-methylpiperazinomethyl)-1H-inden-1-ol
CIS-2,3-dihydro-2-(1-pyrrolidino)-1H-inden-1-ol
CIS-2,3-dihydro-2-(N,N-dimethylaminoethyl)-1H-inden-1-ol
CIS-2-diethylamino-1,2,3,4-tetrahydronaphthalene-1-ol
CIS-2-(dimethylaminomethyl)-1,2,3,4-tetrahydronaphthalen-1-ol

STEP B: CIS-2,3-dihydro-1-(2-methoxyphenoxy)-N,N-dimethyl-1H-indene-2-methanamine

A mixture of 0.75 g of 50% sodium hydride dispersion in oil and 10 ml of dimethylsulfoxide was heated in an oil bath at 65° in a nitrogen atmosphere for 30 minutes and cooled to room temperature. CIS-2,3-dihydro-2-(N,N-dimethylaminomethyl)-inden-1-ol (1.91 g, 0.01 M) was added and the mixture stirred for 15 minutes. 2-Fluoroanisole (3.5 ml) was added and the mixture heated at 90° overnight. After cooling and diluting with water, the product was extracted into ethyl acetate. The amine was isolated by chromatography on silica and elution with 10% ethyl acetate in hexane. Kugelrohr distillation at 123-125°/0.4 mm Hg gave the pure amine.

Anal. Calcd. for $C_{19}H_{23}NO_2$			
Fd:	C = 76.73; C = 76.62;	H-7.80; H = 7.99;	N-4.71 N = 4.98

By procedures analogous to that described above, the following compounds of the formula (1) can be prepared:

CIS-2,3-dihydro-N-methyl-N-(phenylmethyl)-1-(4-trifluoromethylphenoxy)-1H-indene-2-methanamine hydrochloride mp 218°

Anal. Calcd. for $C_{25}H_{24}F_3NO \cdot HCl$			
Fd:	C = 67.03; C = 67.16;	H = 5.63; H = 5.57;	N = 3.13 N = 3.16

CIS-2,3-dihydro-N,N-dimethyl-1-phenoxy-1H-indene-2-methanamine
Bp 110-115°/0.3 mm Hg

Anal. Calcd for $C_{15}H_{21}NO$			
Fd:	C = 80.86; C = 80.58;	H = 7.92; H = 7.93;	N = 5.24 N = 5.01

CIS-2,3-dihydro-N,N-dimethyl-1-(4-trifluoromethylphenoxy)-1H-indene-2-methanamine hydrochloride
mp 178-180°

Anal. Calcd for $C_{19}H_{20}F_3NO \cdot HCl$			
Fd:	C = 61.37; C = 61.23;	H = 5.69; H = 5.79;	N = 3.77 N = 3.70

CIS-1,2,3,4-tetrahydro-1-(2-methoxyphenoxy)-N,N-dimethyl-2-naphthalenemethanamine
Bp 135-140°/0.4 mm Hg

Anal. Calcd for $C_{20}H_{25}NO_2$			
Fd:	C = 77.13; C = 77.02;	H = 8.09; H = 8.05;	N-4.50 N = 4.52

CIS-4-{[2,3-dihydro-1-(2-methoxyphenoxy)-1H-inden-2-yl]methyl}morpholine oxalate
mp 144-145°

Anal. Calcd. for $C_{21}H_{25}NO_3 \cdot C_2H_2O_4$			
Fd:	C = 64.32; C = 64.08;	H = 6.34; H = 6.47;	N-3.26 N = 3.19

CIS-1-(3,4-dichlorophenoxy)-2,3-dihydro-N,N-dimethyl-1H-indene-2-methanamine hydrochloride mp 192-193°

Anal. Calcd for $C_{18}H_{19}Cl_2NO \cdot HCl$			
Fd:	C = 58.00; C = 58.11;	H = 5.41; H = 5.49;	N-3.76 N = 3.68

CIS-6-chloro-2,3-dihydro-1-(2-methoxyphenoxy)-N,N-dimethyl-1H-indene-2-methanamine maleate mp 141-143°

Anal. Calcd. for $C_{19}H_{22}ClNO_2 \cdot C_4H_4O_4$			
Fd:	C = 61.67; C = 61.39;	H = 5.85; H = 5.97;	N = 3.13 N = 3.01

CIS-2,3-dihydro-N,N-dimethyl-1-(2-methylphenoxy)-1H-indene-2-methanamine oxalate
CIS-2,3-dihydro-N,N-dimethyl-1-phenoxy-1H-indene-2-amine
CIS-2,3-dihydro-1-(3,4-dimethoxyphenoxy)-N,N-dimethyl-1H-indene-2-methanamine
CIS-5-(4-fluorophenoxy)-5,6,7,8-tetrahydrobenzocycloheptan-6-methanamine
CIS-1-(3-chlorophenoxy)-2,3-dihydro-3,3,N,N-tetramethyl-6-methoxy-1H-indene-2-methanamine

EXAMPLE 2

CIS and TRANS-1,2,3,4-tetrahydro-1-(2-methoxyphenoxy)-N,N-dimethyl-2-naphthalenemethanamine

A mixture of 8.21g (0.04 M) of TRANS-1,2,3,4-tetrahydro-2-(N,N-dimethylaminomethyl)naphthalen-1-ol, 11.54 g (0.044 M) of triphenyl phosphine, 5.46 g (0.044 M) of 2-methoxyphenol and 100 ml of benzene was stirred and a solution of 7.83 g (0.004 M) of 95% diethyl azodicarboxylate in 25 ml of benzene was added dropwise over 45 minutes. After 2 hours, the mixture was filtered and extracted with cold 3% hydrochloric acid. The acid extracts were made basic with dilute sodium hydroxide and the oil which separated was extracted into ether. The solvent was removed and the residual oil chromatographed on silica gel. Elution with 1:1 ether-chloroform gave the TRANS-isomer - 1.20 g, Bp 135-38°/0.4 mm Hg

Anal. Calcd for $C_{20}H_{25}NO_2$:			
Fd:	C = 77.13; C = 77.15;	H = 8.09; H = 8.21;	N-4.50 N = 4.56

Elution with ether gave the CIS-isomer, 2.64 g. Bp 135-40°/0.4 mm Hg

Anal. Calcd. for $C_{20}H_{25}NO_2$:			
Fd:	C = 77.13; C = 77.02;	H = 8.09; H = 8.05;	N = 4.50 N = 4.52.

EXAMPLE 3

CIS and TRANS-2,3-dihydro-1-(2-methoxyphenoxy)-N,N-dimethyl-1H-inden-2-amine oxalate

A mixture of 1.0 g sodium hydride (50% suspension in oil) and 25 ml of dimethylsulfoxide was heated in an oil bath at 60° for 0.5 hours. The mixture was cooled and 2.22 g (0.013 m) of CIS-2,3-dihydro-2-N,N-dimethylamino-1H-inden-1-ol was added. After stirring 10 minutes, 3.3 g (0.026 M) of 2-fluoroanisol was added and the mixture heated at 90° for 21 hours. After cooling, the mixture was poured into water and extracted with ethyl acetate. Evaporation left an oil which was chromatographed on silica gel. Elution with ethyl acetate gave the TRANS-isomer which was converted into the oxalate salt in ether (0.72 g, m.p. 172-73°).

Anal. Calcd. for $C_{18}H_{21}NO_2 \cdot C_2H_2O_4$			
Fd:	C=64.33; C=64.23;	H-6.21; H=6.29;	N=3.75 N=3.72

The CIS isomer was eluted with 9:1 ethyl acetate-methanol and converted to the oxalate salt in ether - 0.92 g, m.p. 149-50° Fd: C=64.16; H=6.27; N=3.80

The starting materials for the above reaction scheme, i.e., the appropriately substituted amino ketones (2) and aryl fluoride/alcohols, are readily obtained through the use of commonly available reagents modified if required through standard synthetic schemes, procedures and techniques as are well known and appreciated by those of ordinary skill in the art.

For example, the appropriate amino alcohol intermediate for compounds of the formula (1) wherein n is O can be prepared by procedures analogous to that described by Huebner, et al, [J. Org. Chem. 35, 1149 (1970)].

The appropriate amino ketone starting material for compounds of the formula (1) wherein n is O, 1 or 2 can be prepared by procedures analogous to that described in U.S. Patent 2,947,756.

In another embodiment, the present invention provides a method of preparing a medicament for treating depression in a patient in need thereof by administering a therapeutically effective antidepressant amount of one or more compounds of the formula (1). In addition, the present invention provides methods of preparing medicaments for inhibiting synaptic norepinephrine uptake, or of inhibiting synaptic serotonin uptake, or of inhibiting both synaptic norepinephrine and serotonin uptake in a patient in need thereof by administering a therapeutically effective inhibitory amount of one or more compounds of the formula (1).

It is generally accepted by those skilled in the art that compounds such as desipramine, which inhibit synaptic norepinephrine uptake, and compounds such as fluoxetine, which inhibit synaptic serotonin (5-hydroxytryptamine or 5-HT) uptake provide antidepresssant effects upon administration to patients suffering from depression.

As used herein, the term "patient" refers to a warm-blooded animal, such as a mammal, which is suffering from depression. It is understood that dogs, cats, rats, mice, horses, bovine cattle, sheep, and humans are examples of animals within the scope of the meaning of the term.

The term "depression" refers to a disease or an abnormal state or condition characterized clinically by a psychiatric syndrome comprising, for example, a dejected mood, psychomotor retardation, insomnia, weight loss, and the like. Depression is readily diagnosed by a clinical diagnostician using practices and procedures well known and appreciated by those of ordinary skill in the art.

It is believed that there is a general correlation between compounds which have a biological effect of inhibiting synaptic norepinephrine or serotonin uptake and the medical effect of being useful in treating depression in a patient suffering therefrom. As used herein, the term "treating depression" refers to providing an antidepressant effect by relieving one or more clinical signs and symptoms of depression in a patient suffering therefrom.

The present invention provides compounds which inhibit both synaptic norepinephrine and serotonin uptake and are therefore believed to be useful in treating depression by administration to a patient suffering therefrom. Although the compounds of the formula (1) inhibit both synaptic norepinephrine and serotonin uptake, in any individual compound these inhibitory effects may be manifested at the same or vastly different concentrations or doses. As a result, some compounds of the formula (1) are useful in treating depression at doses at which synaptic norepinephrine uptake may be substantially inhibited but at which synaptic serotonin uptake is not substantially inhibited. And, conversely, some compounds of the formula (1) are useful in treating depression at doses at which synaptic serotonin uptake may be substantially

inhibited but at which synaptic norepinephrine uptake is not substantially inhibited. Other compounds of formula (1) are useful in treating depression at doses at which both synaptic norepinephrine and serotonin uptake are substantially inhibited.

The concentrations or doses at which a test compound inhibits synaptic norepinephrine and serotonin uptake is readily determined by the use of standard assay and techniques well known and appreciated by one of ordinary skill in the art. For example, the degree of inhibition at a particular dose in rats can be determined by the method of Dudley, et al., [J. Pharmacol. Exp. Ther. 217, 834-840 (1981)].

The therapeutically effective inhibitory dose is one which is effective in substantially inhibiting synaptic norepinephrine uptake or synaptic serotonin uptake or both synaptic norepinephrine and serotonin uptake. The therapeutically effective inhibitory dose can be readily determined by those skilled in the art by using conventional range finding techniques and analagous results obtained in the test systems described above. The therapeutically effective inhibitory dose will generally be the same as the therapeutically effective antidepressant dose.

A therapeutically effective antidepressant or inhibitory dose can be readily determined by the attending diagnostician, as one skilled in the art, by the use of conventional techniques and by observing results obtained under analogous circumstances. In determining the therapeutically effective dose, a number of factors are considered by the attending diagnostician, including but not limited to: the species of mammal; its size, age, and general health; the specific disease involved; the degree of or involvement or the severity of the disease; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances.

In treating depression or in inhibiting synaptic norepinephrine and/or serotonin uptake, a compound of formula (1) can be administered in any manner which makes the compound bioavailable in effective amounts, including oral and parenteral routes. For example, compounds of the formula (1) can be administered orally, subcutaneously, intramuscularly, intravenously, transdermally, intranasally, rectally, and the like. Oral administration is generally preferred.

A therapeutically effective antidepressant or inhibitory amount of a compound of the formula (1) is expected to vary from about 0.1 milligrams per kilogram of body weight per day (mg/kg/day) to about 100 mg/kg/day. Preferred amounts are expected to vary from about 1 to about 10 mg/kg/day.

The compounds of this invention can be administered in various forms to achieve the desired effect. The compounds which generally are free amines in liquid form can be administered alone or in the form of a pharmaceutical composition in combination with pharmaceutically acceptable carriers or excipients, the proportion and nature of which are determined by the solubility and chemical properties of the compound selected, the chosen route of administration, and standard pharmaceutical practice. The compounds of the invention, while effective themselves, may also be formulated and administered in the form of their acid addition salts for purposes of stability, convenience of crystallization, increased solubility and the like where these salts are pharmaceutically acceptable.

In another embodiment, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of the formula (1) in admixture or otherwise in association with one or more pharmaceutically acceptable carriers or excipients. The term "therapeutically effective amount" refers to therapeutically effective antidepressant or inhibitory amount as appropriate.

The pharmaceutical compositions are prepared in a manner well known *per se* in the pharmaceutical art. The carrier or excipient may be solid, semi-solid, or liquid material which can serve as a vehicle or medium for the active ingredient. Suitable carriers or excipients are well known in the art *per se*. The pharmaceutical composition may be adapted for oral or parenteral use and may be administered to the patient in the form of tablets, capsules, suppositories, solution, suspensions, or the like.

The compounds of the present invention may be administered orally, for example, with an inert diluent or with an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compounds may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like. These preparations should contain at least 4% of the compound of the invention, the active ingredient, but may be varied depending upon the particular form and may conveniently be between 4% to about 70% of the weight of the unit. The amount of the compound present in compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that an oral dosage unit form contains between 5.0-300 milligrams of a compound of the invention.

The tablets, pills, capsules, troches and the like may also contain one or more of the following adjuvants; binders such as microcrystalline cellulose, gum tragacanth or gelatin; excipients such as starch or lactose, disintegrating agents such as alginic acid, Primogel, cornstarch and the like; lubricants such as

magnesium stearate or Sterotex; glidants such as colloidal silicon dioxide; and sweetening agents such as sucrose or saccharin may be added or a flavoring agent such as peppermint, methyl salicylate or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or a fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the present compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral therapeutic administration, the compounds of the present invention may be incorporated into a solution or suspension. These preparations should contain at least 0.1% of a compound of the invention, but may be varied to be between 0.1 and about 50% of the weight thereof. The amount of the inventive compound present in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that a parenteral dosage unit contains between 5.0 to 100 milligrams of the compound of the invention.

The solutions or suspensions may also include the one or more of the following adjuvants: sterile diluents such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylene diaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

As with any group of structurally related compounds which possess a particular generic utility, certain groups and configurations are preferred for compounds of the formula (1) in their end-use application.

Compounds of the formula (1) which function as essentially equipotent inhibitors of synaptic norepinephrine and serotonin uptake are generally preferred. Essentially equipotent inhibitors are those which inhibit synaptic norepinephrine and serotonin uptake at substantially the same concentrations or at substantially the same doses (i.e., the therapeutically effective inhibitory dose for synaptic norepinephrine uptake and for synaptic serotonin uptake are substantially equivalent).

Furthermore, compounds of the formula (1) wherein R_2 is methyl and R_3 is hydroxy and those wherein R_2 and R_3 are each methyl are preferred. Compounds wherein n is 1 are generally preferred. Compounds wherein R_1 is $-CH_2-$ or $-CH_2CH_2-$ are preferred. Compounds wherein p and q are O are also generally preferred. For compounds wherein p is 1, chloro is preferred for Y. For compounds wherein q is 1, CF_3, methoxy and chloro are preferred for X.

The following compounds are particularly preferred embodiments of the present invention:

2,3-dihydro-1-(2-methoxyphenoxy)-N,N-dimethyl-1H-indene-2-methanamine,

2,3-dihydro-N-methyl-1-[4-(trifluoromethyl)phenoxy]-1H-indene-2-methanamine hydrochloride.

As a further embodiment of the present invention, an improvement is provided in the method of preparing a medicament for treating depression in a patient in need thereof. This improvement comprises providing a medicament that inhibits both synaptic norepinephrine uptake and synaptic serotonin uptake in the depressed patient. This improved treatment allows administering a therapeutically effective inhibitory amount of a compound of the invention which functions as both a synaptic nerepinephrine and serotonin uptake inhibitor.

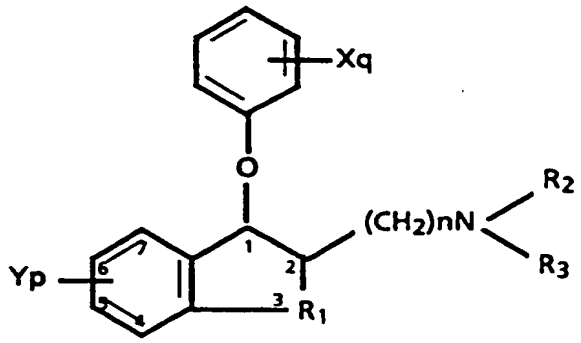
Surprisingly, applicants now have found that inhibition of both synaptic norepinephrine and serotonin uptake in a patient suffering from depression has a synergistic beneficial effect in effecting a down-regulation of β-adrenergic receptors and therefore believe that this treatment will provide a significant improvement in the treatment of depression.

The compounds of the present invention function as both synaptic norepinephrine uptake inhibitors and synaptic serotonin uptake inhibitors. Administration of compounds which function as essentially equipotent inhibitors of synaptic norepinephrine and serotonin uptake is preferred.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A compound of the formula



wherein

R_1	is a C_1-C_3 alkylene,
n, p and q	are each independently 0, 1 or 2,
Y and X	are each independently (C_1-C_6)alkyl, (C_1-C_6) alkoxy, hydroxy, CF_3, halogeno or when p or q are 2 and each of the Y or each of the X groups are on adjacent aryl carbon atoms, both of the X or both of the Y groups can be taken together to form a methylenedioxy moiety,
R_2 and R_3	are each independently hydrogen, (C_1-C_6) alkyl, aralkyl,or R_2 and R_3 taken together with the nitrogen to which they are attached are pyrrolidino, morpholino, piperidino, piperazino, or 4-methylpiperazino,

or an acid addition salt thereof.

2. A compound of claim 1 wherein R_2 is methyl and R_3 is hydroxy.

3. A compound of claim 1 wherein R_2 and R_3 are each methyl.

4. A compound of claim 1 wherein R_1 is $-CH_2-$ or $-CH_2CH_2-$.

5. a compound of claim 1 wherein n is 1.

6. A compound of claim 1 wherein p is O.

7. A compound of claim 1 wherein Y is chloro and p is 1.

8. A compound of claim 1 wherein X is CF_3 and q is 1.

9. A compound of claim 1 wherein X is methoxy and q is 1.

10. A compound of claim 1 wherein q is O.

11. A compound of claim 1 wherein X is chloro and q is 1.

12. 2,3-dihydro-1-(2-methoxyphenoxy)-N,N-dimethyl-1H--indene-2-methanamine.

13. 2,3-dihydro-N-methyl-1-/4-(trifluoromethyl)-phenoxy/-1H-indene-2-methanamine hydrochloride.

14. A pharmaceutical composition comprising a compound of any one of the preceeding claims in admixture with a pharmaceutically acceptable carrier.

15. A compound according to any one of claims 1 to 13 for use as a medicine.

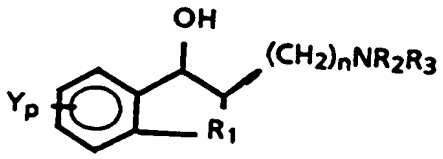
16. Use of a compound of any one of claims 1 to 13 for preparing a medicament for treating depression or for inhibiting serotonin and/or norepinephrine uptake.

17. A product containing:
a) a compound of claim 1 which functions as a serotonin uptake inhibitor and
b) a compound of claim 1 which functions as a norepinephrine uptake inhibitor,
for conjunctive therapy of depression.

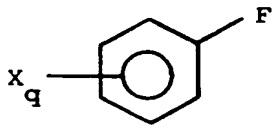
18. A pharmaceutical composition containing:
a) a compound of claim 1 which functions as a serotonin uptake inhibitor, and
b) a compound of claim 1 which functions as a norepinephrine uptake inhibitor,
and a pharmaceutically acceptable carrier.

19. A product of claim 17 wherein a single active compound functions both as a serotonin and norepinephrine uptake inhibitor.

20. A proces for preparing a compound of any one of claims 1 to 13 which comprises reacting a benzocycloalkanamine-1-ol of formula



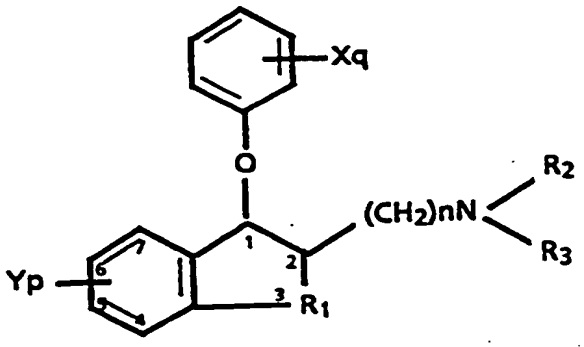
wherein Yp, n, R_1, R_2, R_3 are as defined above with an aryl fluoride of formula



wherein Xq is defined as above.

Claims for the following Contracting States : GR, ES

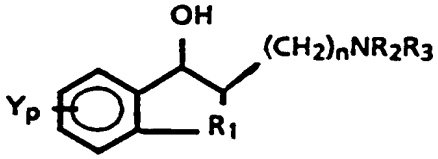
1. A process for preparing a compound of the formula



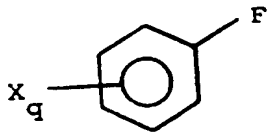
wherein

R_1	is a C_1-C_3 alkylene,
n, p and q	are each independently 0, 1 or 2,
Y and X	are each independently(C_1-C_6)alkyl, (C_1-C_6) alkoxy, hydroxy, CF_3, halogeno or when p or q are 2 and each of the Y or each of the X groups are on adjacent aryl carbon atoms, both of the X or both of the Y groups can be taken together to form a methylenedioxy moiety,
R_2 and R_3	are each independently hydrogen, (C_1-C_6) alkyl, aralkyl,or R_2 and R_3 taken together with the nitrogen to which they are attached are pyrrolidino, morpholino, piperidino, piperazino, or 4-methylpiperazino,

or an acid addition salt thereof which comprises reacting benzocycloalkanamine-1-ol of the formula



wherein Yp, Rn, R_1, R_2, R_3 are as defined above with an aryl fluoride of formula



wherein Xq us defined as above.

2. A process according to claim 1 for preparing a compound wherein R_2 is methyl and R_3 is hydroxy.

3. A process according to claim 1 for preparing a compound wheren R_2 and R_3 are each methyl.

4. A process according to claim 1 for preparing a compound wherein R_1 is $-CH_2-$ or $-CH_2CH_2-$.

5. A process according to claim 1 for preparing a compound wherein n is 1.

6. A process according to claim 1 for preparing a compound wherein p is O.

7. A process according to claim 1 for preparing a compound wherein Y is chloro and p is 1.

8. A process according to claim 1 for preparing a compound wherein X is CF_3 and q is 1.

9. A process according to claim 1 for preparing a compound wherein X is methoxy and q is 1.

10. A process according to claim 1 for preparing a compound wherein q is 0.

11. A process according to claim 1 for preparing a compound wherein X is chloro and q is 1.

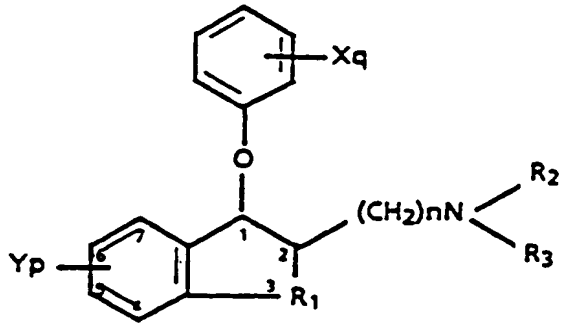
12. A process according to claim 1 for preparing 2,3-dihydro-1-(2-methoxyphenoxy)-N,N-dimethyl-1H--indene-2-methanamine.

13. A process according to claim 1 for preparing 2,3-dihydro-N-methyl-1-/4-(trifluoromethyl)-phenoxy/-1H-indene-2-methanamine hydrochloride.

14. Use of a compound of anyone of claims 1 to 13 for preparing a medicament for treating depression or for inhibiting serotonin and/or norepinephrine uptake.

Patentansprüche
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verbindung der Formel



worin

R_1	eine C_1-C_3 -Alkylenkette bedeutet,
n, p und q	unabhängig voneinander 0, 1 oder 2 bedeuten,
Y und X	unabhängig voneinander eine (C_1-C_6)-Alkyl-, (C_1-C_6)-Alkoxygruppe, einen Hydroxy- oder CF_3-Rest oder ein Halogenatom bedeuten, oder, falls p oder q für 2 stehen und jede der Y- oder jede der X-Gruppen an benachbarte Arylkohlenstoffatome gebunden sind, beide X- oder beide Y-Gruppen zusammen einen Methylendioxyrest bilden können,
R_2 und R_3	unabhängig voneinander Wasserstoffatome oder (C_1-C_6)-Alkyl- oder Aralkylgruppen oder R_2 und R_3 zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen Pyrrolidino-, Morpholino-, Piperidino-, Piperazino- oder 4-Methylpiperazinorest bedeuten,

oder ein Säureadditionssalz davon.

2. Verbindung nach Anspruch 1, worin R_2 einen Methylrest und R_3 einen Hydroxyrest bedeuten.

3. Verbindung nach Anspruch 1, worin R_2 und R_3 je einen Methylrest bedeuten.

4. Verbindung nach Anspruch 1, worin R_1 für $-CH_2-$ oder $-CH_2CH_2-$ steht.

5. Verbindung nach Anspruch 1, worin n für 1 steht.

6. Verbindung nach Anspruch 1, worin p für 0 steht.

7. Verbindung nach Anspruch 1, worin Y ein Chloratom bedeutet und p für 1 steht.

8. Verbindung nach Anspruch 1, worin X einen CF_3-Rest bedeutet und q für 1 steht.

9. Verbindung nach Anspruch 1, worin X einen Methoxyrest bedeutet und q für 1 steht.

10. Verbindung nach Anspruch 1, worin q für 0 steht.

11. Verbindung nach Anspruch 1, worin X ein Chloratom bedeutet und q für 1 steht.

12. 2,3-Dihydro-1-(2-methoxyphenoxy)-N,N-dimethyl-1H-inden-2-methanamin.

13. 2,3-Dihydro-N-methyl-1-[4-(trifluormethyl)phenoxy]-1H-inden-2-methanamin-hydrochlorid.

14. Pharmazeutische Zusammensetzung, enthaltend eine Verbindung nach einer der vorhergehenden Ansprüche in Mischung mit einem pharmazeutisch verträglichen Träger.

15. Verbindung nach einem der Ansprüche 1 bis 13 zur Verwendung als Arzneistoff.

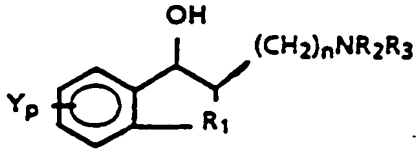
16. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 13 zur Herstellung eines Medikaments zur Depressionsbehandlung oder zur Hemmung der Serotonin- und/oder Norepinephrin-Aufnahme.

17. Produkt, enthaltend:
a) eine Verbindung nach Anspruch 1, die als Hemmer der Serotonin-Aufnahme wirkt und
b) eine Verbindung nach Anspruch 1, die als Hemmer der Norepinephrin-Aufnahme wirkt
für eine kombinierte Depressionsbehandlung.

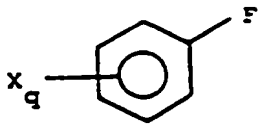
18. Pharmazeutische Zusammensetzung, enthaltend:
a) eine Verbindung nach Anspruch 1, die als Hemmer der Serotonin-Aufnahme wirkt und
b) eine Verbindung nach Anspruch 1, die als Hemmer der Norepinephrin-Aufnahme wirkt
und einen pharmazeutisch verträglichen Träger.

19. Produkt nach Anspruch 17, worin eine einzelne aktive Verbindung als Hemmer sowohl der Serotonin- als auch der Norepinephrin-Aufnahme wirkt.

20. Verfahren zur Herstellung einer Verbindung nach einem der Ansprüche 1 bis 13, enthaltend das Umsetzen eines Benzocycloalkanamin-1-ols der Formel



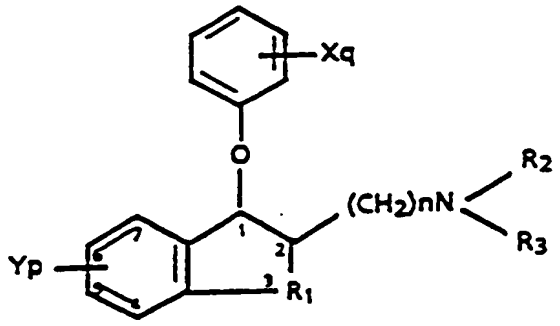
worin Yp, n, R_1, R_2 und R_3 wie oben definiert sind, mit einem Arylfluorid der Formel



worin Xq wie oben definiert ist.

Patentansprüche für folgende Vertragsstaaten : GR, ES

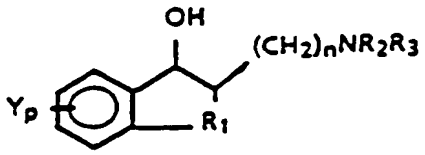
1. Verfahren zur Herstellung einer Verbindung der Formel



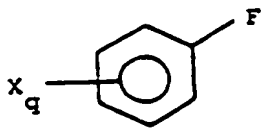
worin

R_1	eine C_1-C_3-Alkylenkette bedeutet,
n, p und q	unabhängig voneinander 0, 1 oder 2 bedeuten,
Y und X	unabhängig voneinander eine (C_1-C_6)-Alkyl-, (C_1-C_6)-Alkoxygruppe, einen Hydroxy- oder CF_3-Rest oder ein Halogenatom bedeuten, oder, falls p oder q für 2 stehen und jede der Y- oder jede der X-Gruppen an benachbarte Arylkohlenstoffatome gebunden sind, beide X- oder beide Y-Gruppen zusammen einen Methylendioxyrest bilden können,
R_2 und R_3	unabhängig voneinander Wasserstoffatome oder (C_1-C_6)-Alkyl- oder Aralkylgruppen oder R_2 und R_3 zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen Pyrrolidino-, Morpholino-, Piperidino-, Piperazino- oder 4-Methylpiperazinorest bedeuten,

oder eines Säureadditionssalzes davon, umfassend das Umsetzen eines Benzocycloalkanamin-1-ols der Formel



worin Yp,Rn, R_1, R_2 und R_3 wie oben definiert sind, mit einem Arylfluorid der Formel



worin Xq wie oben definiert ist.

2. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung, worin R_2 ein Methylrest und R_3 ein Hydroxyrest sind.

3. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung, worin R_2 und R_3 je ein Methylrest sind.

4. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung, worin R_1 $-CH_2-$ oder $-CH_2CH_2-$ ist.

5. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung, worin n eine 1 ist.

6. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung, worin p eine 0 ist.

7. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung, worin Y ein Chloratom ist und p eine 1 ist.

8. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung, worin X ein CF_3-Rest ist und q eine 1 ist.

9. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung, worin X ein Methoxyrest ist und q eine 1 ist.

10. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung, worin q eine 0 ist.

11. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung, worin X ein Chloratom ist und q eine 1 ist.

12. Verfahren nach Anspruch 1 zur Herstellung von 2,3-Dihydro-1-(2-methoxyphenoxy)-N,N-dimethyl-1H-inden-2-methanamin.

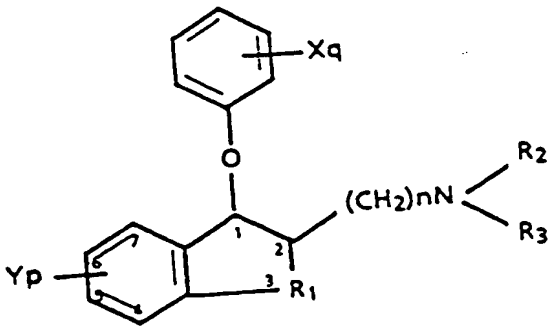
13. Verfahren nach Anspruch 1 zur Herstellung von 2,3-Dihydro-N-methyl-1-[4-(trifluormethyl)phenoxy]-1H-inden-2-methanamin-hydrochlorid.

14. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 13 zur Herstellung eines Medikaments zur Depressionsbehandlung oder zur Hemmung der Serotonin- und/oder Norepinephrin-Aufnahme.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Un composé de formule :



dans laquelle :

R_1 est un groupe C_1-C_3 alkylène,

n, p et q désignent chacun indépendamment 0, 1 ou 2,

Y et X désignent chacun indépendamment un groupe (C_1-C_6)alkyle, (C_1-C_6)alcoxy, hydroxy, CF_3, halogéno ou lorsque p ou q est égal à 2 et que chacun des groupes Y ou X sont sur des atomes de carbone aryliques adjacents, tous les deux groupes X ou tous les deux groupes Y peuvent être pris ensemble pour former une portion méthylènedioxy,

R_2 et R_3 désignent chacun indépendamment un atome d'hydrogène, un groupe (C_1-C_6)alkyle, aralkyle, ou bien R_2 et R_3 pris ensemble avec l'atome d'azote auquel ils sont attachés forment un

groupe pyrrolidino, morpholino, pipéridino, pipérazino ou 4-méthylpipérazino,
ou un sel d'addition d'acide dudit composé.

2. Un composé selon la revendication 1, selon laquelle R_2 est un groupe méthyle et R_3 est un groupe hydroxy.

3. Un composé selon la revendication 1, selon laquelle R_2 et R_3 sont chacun un groupe méthyle.

4. Un composé selon la revendication 1, selon laquelle R_1 est un groupe $-CH_2-$ ou $-CH_2CH_2-$.

5. Un composé selon la revendication 1, selon laquelle n est égal à 1.

6. Un composé selon la revendication 1, selon laquelle p est égal à 0.

7. Un composé selon la revendication 1, selon laquelle Y est un groupe chloro et p est égal à 1.

8. Un composé selon la revendication 1, selon laquelle X est un groupe CF_3 et q est égal à 1.

9. Un composé selon la revendication 1, selon laquelle X est un groupe méthoxy et q est égal à 1.

10. Un composé selon la revendication 1, selon laquelle q est égal à 0.

11. Un composé selon la revendication 1, selon laquelle X est un groupe chloro et q est égal à 1.

12. 2,3-dihydro-1-(2-méthoxyphénoxy)-N,N-diméthyl-1H-indène-2-méthanamine.

13. 2,3-dihydro-N-méthyl-1-/4-(trifluorométhyl)phénoxy/-1H-indène-2-méthanamine, chlorhydrate.

14. Une composition pharmaceutique comprenant un composé selon l'une quelconque des revendications précédentes en mélange avec un support pharmaceutiquement acceptable.

15. Un composé selon l'une quelconque des revendications 1 à 13 à utiliser comme médicament.

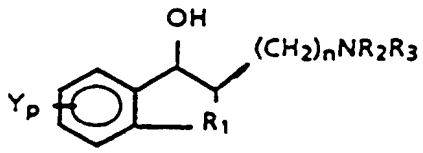
16. Utilisation d'un composé selon l'une quelconque des revendications 1 à 13 pour la préparation d'un médicament pour le traitement de la dépression ou pour l'inhibition de la fixation de la sérotonine et/ou de la norépinéphrine.

17. Un produit contenant :
a) un composé selon la revendication 1 qui agit comme inhibiteur de la fixation de la sérotonine et
b) un composé selon la revendication 1 qui agit comme inhibiteur de la fixation de la norépinéphrine,
pour la thérapie conjonctive de la dépression.

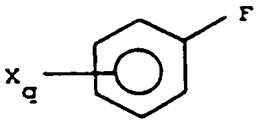
18. Une composition pharmaceutique contenant :
a) un composé selon la revendication 1 qui agit comme inhibiteur de la fixation de la sérotonine, et
b) un composé selon la revendication 1 qui agit comme inhibiteur de la fixation de la norépinéphrine,
et un support pharmaceutiquement acceptable.

19. Un produit selon la revendication 17, selon laquelle un seul composé actif agit à la fois comme inhibiteur de la fixation de la sérotonine et comme inhibiteur de la fixation de la norépinéphrine.

20. Un procédé de préparation d'un composé selon l'une quelconque des revendications 1 à 13 qui comprend la réaction d'un benzocycloalcanamine-1-ol de formule :



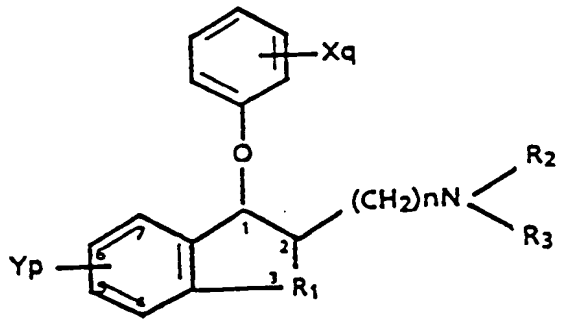
dans laquelle Yp, n, R_1, R_2, R_3 sont comme définis précédemment avec un fluorure d'aryle de formule :



dans laquelle Xq est comme défini précédemment.

Revendications pour les Etats contractants suivants : GR, ES

1. Un procédé de préparation d'un composé de formule :



dans laquelle :

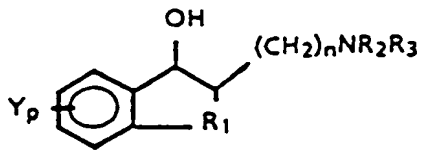
R_1 est un groupe C_1-C_3 alkylène,

n, p et q désignent chacun indépendamment 0, 1 ou 2,

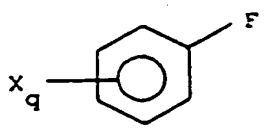
Y et X désignent chacun indépendamment un groupe (C_1-C_6)alkyle, (C_1-C_6)alcoxy, hydroxy, CF_3, halogéno ou lorsque p ou q est égal à 2 et que chacun des groupes Y ou X sont sur des atomes de carbone aryliques adjacents, tous les deux groupes X ou tous les deux groupes Y peuvent être pris ensemble pour former une portion méthylènedioxy,

R_2 et R_3 désignent chacun indépendamment un atome d'hydrogène, un groupe (C_1-C_6)alkyle, aralkyle, ou bien R_2 et R_3 pris ensemble avec l'atome d'azote auquel ils sont attachés forment un groupe pyrrolidino, morpholino, pipéridino, pipérazino ou 4-méthylpipérazino,

ou d'un sel d'addition d'acide de ce composé qui consiste à faire réagir un benzocycloalcaneamine-1-ol de formule :



dans laquelle Yp, Rn, R_1, R_2, R_3 sont comme définis précédemment avec un fluorure d'aryle de formule :



dans laquelle Xq est comme défini précédemment.

2. Un procédé selon la revendication 1 pour la préparation d'un composé dans lequel R_2 est un groupe méthyle et R_3 est un groupe hydroxy.

3. Un procédé selon la revendication 1 pour la préparation d'un composé dans lequel R_2 et R_3 sont chacun un groupe méthyle.

4. Un procédé selon la revendication 1 pour la préparation d'un composé dans lequel R_1 est un groupe $-CH_2-$ ou $-CH_2CH_2-$.

5. Un procédé selon la revendication 1 pour la préparation d'un composé dans lequel n est égal à 1.

6. Un procédé selon la revendication 1 pour la préparation d'un composé dans lequel p est égal à 0.

7. Un procédé selon la revendication 1 pour la préparation d'un composé dans lequel Y est un groupe chloro et p est égal à 1.

8. Un procédé selon la revendication 1 pour la préparation d'un composé dans lequel X est un groupe CF_3 et q est égal à 1.

9. Un procédé selon la revendication 1 pour la préparation d'un composé dans lequel X est un groupe méthoxy et q est égal à 1.

10. Un procédé selon la revendication 1 pour la préparation d'un composé dans lequel q est égal à 0.

11. Un procédé selon la revendication 1 pour la préparation d'un composé dans lequel X est un groupe chloro et q est égal à 1.

12. Un procédé selon la revendication 1 pour la préparation de la 2,3-dihydro-1-(2-méthoxyphénoxy)-N,N-diméthyl-1H-indène-2-méthanamine.

13. Un procédé selon la revendication 1 pour la préparation du 2,3-dihydro-N-méthyl-1-/4-(trifluorométhyl)-phénoxy/-1H-indène-2-méthanamine, chlorhydrate.

14. Utilisation d'un composé selon l'une quelconque des revendications 1 à 13 pour la préparation d'un médicament pour le traitement de la dépression ou pour l'inhibition de la fixation de la sérotonine et/ou de la norépinéphrine.